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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/707,147	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/06; 10/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, claims 1-10, 13, 14 and 16, as well as the target gene BIKE, which has the sequence of SEQ ID NO: 2961, in the reply filed on 11/6/2006 is acknowledged. Applicant has cancelled claims 1-16 and added claims 17-36, which are directed to the elected invention.

Applicant further elects SEQ ID NO: 48 with traverse. Applicant asserts that it has been determined that normally ten sequences constitute a reasonable number for examination purposes absent an exceptional case. Contrary to applicant's assertion, the examination guidelines referred to by applicant determined that "up to ten sequences" are reasonable, rather than ten sequences, as asserted by applicant. Each of the instant sequences are structurally unique, each comprising a distinct sequence of nucleotides, each having no common structural core. To search for more than one of the sequences in the same application would present an undue search and corresponding examination burden. Furthermore, see http://www.uspto.gov/web/patents/patog/week13/OG/TOC.htm#ref14, wherein the document explains the rescission of the 1996 Notice that allowed up to ten independent and distinct sequences for search and examination in an application.

The requirement is still deemed proper and is therefore made FINAL. Instant claims 17-36 are examined herein as the elected invention, since the claims are all directed to SEQ ID NO: 48 or SEQ ID NO: 354, a single sequence contained within SEQ ID NO: 48.

Information Disclosure Statement

The two information disclosure statements submitted on 10/3/06 have been considered by the examiner.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The disclosure of the prior-filed applications fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed applications do not teach an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence comprises (a) at least 18 consecutive nucleotides of SEQ ID NO: 48; (b) an RNA equivalent of (a); (c) a sequence at least 64/84 identical to (a) or (b); or (d) the complement of any one of (a)-

(c). Furthermore, the applications do not teach that the at least 18 consecutive nucleotides comprise the sequence of SEQ ID NO: 354.

Therefore, the instant claims are accorded an effective filing date of 11/24/2003, the filing date of the instant application. Should applicant disagree, applicant is encouraged to point out with particularity by page and line number where such support might exist for each claim limitation in each of the priority documents.

Claim Objections

Claims 21, 24, 26 and 28 are objected to because of the following informalities: Claim 21 recites plural "SEQ ID NOS" although the claim only recites one sequence, SEQ ID NO: 354. Claims 24, 26 and 28 are objected to because they depend from claim 21. Recitation of "SEQ ID NO: 354", would obviate this objection. Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility.

The claims are drawn to an isolated nucleic acid sequence consisting of 18 to 120 nucleotides, wherein the sequence comprises a) at least 18 consecutive nucleotides of SEQ ID NO: 48; b) an RNA equivalent of (a); c) a sequence at least 64/84 identical to (a) or (b); or d) the complement of any one of (a)-(c).

Also claimed are vectors, probes and expression systems thereof.

Applicant further claims SEQ ID NO: 354, corresponding to a 22-nucleotide sequence contained within SEQ ID NO: 48.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation (see paragraph [0006]).

The specification discloses that "MIR genes are regulatory genes encoding microRNA's (miRNA), short ~22 nt non-coding RNAs, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell differentiation" (see paragraph [0006]). The specification discloses, "The present invention relates to a novel groups of regulatory, non-protein coding genes, which are functional in specifically inhibiting translation of target proteins. Each gene in this novel group of genes, here identified as GAM or Genomic Address Messengers, specifically inhibits translation of one or more other 'target' genes by means of complementary

hybridization of a segment of the RNA transcript encoded by GAM, to an inhibitor site located in an untranslated region (UTR) of the mRNA of the one or more 'target' genes" (see paragraph [0010]).

The specification discloses that SEQ ID NO: 1 through SEQ ID: 20189 represent genomic sequences of the present invention and that the genomic sequences designated SEQ ID NO: 1 through SEQ ID NO: 200 are nucleotide sequences of 200 gene precursors of respective novel genes of the present invention and genomic sequences designated SEQ ID NO: 201 through SEQ ID NO: 400 are nucleotide sequences of 199 genes of the present invention (see paragraph [0060]).

The specification discloses that GAM is a novel bioinformatically detectable regulatory, non-protein coding, micro RNA (miRNA) gene (see paragraph [0090]). The specification discloses that GAMs represent precursor miRNAs or miRNA-like sequences encoded by a bacterial and/or human genome. Such sequences are predicted to have a hairpin like structure and to give rise to short, ~22-nt RNAs, which presumably provide gene repression activity.

The specification teaches how to detect and validate the expression of GAMs in cells. The specification discloses that GAM genes encode GAM precursor RNAs, which have structural similarities to miRNA genes. The specification teaches that the GAM precursors look like miRNA genes because they don't encode a protein and they have two-dimensional hairpin like structure, which is typical of RNA encoded by miRNA genes (see paragraph [0093]).

The specification discloses "It is appreciated that specific functions and accordingly utilities of a plurality of GAM genes described by Fig. 8 correlate with, and may be deduced from the identity of the target genes that each of said plurality of GAM genes binds and inhibits, and the function of each of said target genes, as elaborated hereinbelow" (see paragraph [0104]). Figure 8 depicts a general schematic of predicted GAM gene function.

The specification discloses that the present invention discloses 200 novel genes of the GAM group of genes, which have been detected bioinformatically and 1096 novel genes of GR group of genes, which have been detected bioinformatically. The GR genes are disclosed as each encoding a plurality of GAM genes. The specification discloses that Fig. 19 illustrates different utilities of genes of the novel group of genes of the present invention. The specification discloses that a function of GAM genes and GR genes is modulation of expression of target genes related to known diseases, and that therefore utilities of the novel genes of the present invention include diagnosis and treatment of the diseases (see paragraph [0186]).

The specification discloses "In summary, the current invention discloses a very large number of novel GR genes, each of which encodes a plurality of GAM genes, which in turn may modulate expression of a plurality of target proteins" (see paragraph [0183]).

However, the specification provides no evidence for these assertions. Moreover, the specification discloses a multitude of sequences that have similar structural characteristics such as secondary hairpin folding to MIR precursor hairpins. However,

the specification does not provide any evidence for a utility of the instantly recited sequences, SEQ ID NOs: 48 and 354. Applicant is broadly asserting a utility for a multitude of sequences based on miRNA-like structure.

Indeed, the asserted utility of these and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. There is no evidence verifying the expression of instant SEQ ID NO: 48 comprising SEQ ID NO: 354 in any cell line much less a human cell line or that its expression or absence thereof has been correlated any disease, bacterial or otherwise, or trait.

Further, Applicant has not provided evidence that instant SEQ ID NO: 48 is up or down regulated in any cell or tissue, animal or bacteria, or plays any role in the predisposition of human or mammalian cells to infection.

Applicant's asserted utility appears to be based only on the predicted structure and sequence complementarity of sequences meeting the criteria of "GAM" sequences and on various reports in the prior art describing various genes and their correlation to diseases. From this, Applicant appears to extrapolate and thereby assert that inhibiting or somehow altering a target gene is beneficial, and that because SEQ ID NO: 48 has a predicted miRNA-like precursor structure and a sequence that is complementarity to some target sequence, it plays a role in inhibiting a target gene and treating a disease.

However, this assertion is not credible. While sequences within SEQ ID NO: 48 may have complementarity to a gene, applicant has not presented any evidence or established any nexus that SEQ ID NO: 48 does target and/or inhibit a specific gene, much less that the expression or inhibition of expression of SEQ ID NO: 48 may be used to prevent or treat a disease associated with a target sequence. The asserted utility is speculative.

While the asserted utility may be credible and specific, it is not substantial. The specification does not establish a nexus between any particular disease state, bacterial process, or host cell process, and an altered level or form of the claimed SEQ ID NO: 48 that would enable one of skill to use SEQ ID NO: 48 to achieve a beneficial effect.

In addition to the bioinformatically predicted utility, described above, the specification generally asserts that Genomic Address Messenger sequences such as instant SEQ ID NO: 48 may be used in various ways. However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

For example, the specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and bacterial diseases, for disease diagnosis and prevention purposes, and for monitoring disease progress.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO: 48, aside from indicating that it may be expressed in certain cells or present in certain genomes, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO: 48 expression for any particular purpose aside from general

research. Further, since applicant does not identify whether abnormal SEQ ID NO: 48 expression is causally related to any disease or condition, or whether abnormal SEQ ID NO: 48 (e.g., a polymorphism) predisposes anyone to any disease or condition such as infection, the only recognizable utility of diagnostic probes is as tools for scientific research, and with no indication that anything useful will be discovered. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the probes or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO: 48, much less the recited RNA equivalents thereof have any specific biological function. No evidence or information is found either in the specification or the prior art linking SEQ ID NO: 48 with the modulation of any bacterial or mammalian gene or with the conditions that render cells or hosts susceptible to any bacterial infection, for example. No convincing evidence is found teaching any biological function for SEQ ID NO: 48 at all. In fact, no evidence is found suggesting or stating that

SEQ ID NO: 48 has been made, isolated, cloned, detected, expressed, or even analyzed in a living cell *in vitro* or *in vivo.*

The specification teaches that GAM7553 gene encodes a GAM7553 precursor RNA that is similar to other miRNA genes because it does not encode a protein. The specification teaches that instant SEQ ID NO:48 is identical or highly similar to the nucleotide sequence of GAM7553 precursor RNA (see paragraph [50905]).

In summary, no biological or biochemical function has been assigned to SEQ ID NO: 48, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA precursor based on folding and have some direct or indirect relation to bacterial disease and/or life cycle.

Thus, Applicant has not demonstrated that SEQ ID NO: 48 may be used in any mode of therapy or as a general means to define and treat bacterial infections.

Thus, the proposed utility of SEQ ID NO: 48 as a therapeutic target or agent, or material resource for preparing diagnostic probes, vectors, a host cells, are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotide.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> ...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for SEQ ID NO: 48, much less any of the RNA equivalents or complements of SEQ ID NO: 48. No target gene has been conclusively identified nor has any evidence been presented linking SEQ ID NO: 48 or fragments thereof with any target gene, bacterial disease or infection, biological function or disorder. A credible, specific, and substantial nexus has not been established.

***

Claims 17-36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, claims 25 and 26 recite that the nucleic acid is capable of modulating expression of a target gene. The specification does not provide evidence that nucleic acids with the structural characteristics of the instantly recited claims are capable of modulating the expression of a target gene, as explained above. Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO: 48, much less the recited RNA equivalents thereof have any specific biological function.

Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is directed to an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence of the nucleic acid "comprises" (a), (b), (c) or (d). Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). Ex parte Markush sanctions claiming a genus expressed as a group consisting of certain specified materials. It appears that the instant claims are directed to a Markush group. However, It is improper to use the term "comprising" instead of "consisting of." (see MPEP 2173.05(h)).

Furthermore, claim 20 is indefinite as it recites "consists of" "(a) at least...". The metes and bounds or consisting of, which is closed language, followed by "at least" is indefinite.

Claims 18-36 are rejected because they depend from claim 17. Claims 21, 22, 24-28, 30, 32, 34 and 36 are also rejected because they depend from claim 20 and claim 20 is considered indefinite, as explained above.

Claims 18, 23, 25, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation "the at least 18 nucleotides" in claim 17. There is insufficient antecedent basis for this limitation in the claim. Recitation of "at least 18 consecutive nucleotides" would obviate this rejection. Claims 23, 25 and 27 are rejected because they depend from claim 18.

Claims 17-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 20 recite "an RNA equivalent of" a nucleic acid sequence comprising at least 18 consecutive nucleotides of SEQ ID NO: 48.

The scope and meaning the term "an RNA equivalent" is unclear. Neither the claims nor the specification clearly defines the meaning of the term "equivalent" as it is to be understood in the context of the instantly claimed invention—that is, no guidance is given as to whether equivalency is based on structure, function, or both.

Thus, one of skill in the art would not be adequately apprised of the metes and bounds of the instant claims.

Claims 18, 19 and 21-36 are rejected for the same reason due to their dependency on claims 17 or 20.

Claims 17-36 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the scope and meaning of the limitations "a sequence at least 64/84 identical to (a) or (b)" or "a sequence at least 64/84 nucleotides identical to (a) or (b)"in claims 17 and 20, respectively, and "at least 14/30 complementary to a binding site sequence of 18 to 24 nucleotides of a target gene" in claims 27 and 28 is not understood.

The meaning of the terms or values "64/84" and "14/30" is unclear since the limitations do not provide any units of measure such as percent, and because the terms or values appear to be inconsistent with the recited length of the claimed nucleic acids. At least two interpretations are possible, wherein "64/84" refers to either the percent identity or the number of nucleotides in common with SEQ ID NO: 48. If "64/84" is interpreted to refer to the number of nucleotides in common, it is unclear how the lower range of 18 to 63-nucleotide nucleic acids can meet this limitation. Similar problems and inconsistencies arise when one attempts to interpret the metes and bounds of the limitation "14/30" in claims 27 and 28.

Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claims are directed to an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence comprises (a) at least 18 consecutive nucleotides of SEQ ID NO: 48; (b) an RNA equivalent of (a); (c) a sequence at least 64/84 identical to (a) or (b); or (d) the complement of any one of (a)-(c). Furthermore, the claims recite that the at least 18 consecutive nucleotides comprises the sequence of SEQ ID NO: 354.

However, the specification does not contemplate each of the above limitations that were newly introduced into the claims filed on 11/6/06. In applicant's arguments filed 11/6/06, applicant points to claims 1-3 and paragraph 0015 of the application as originally filed for support for the limitation "nucleic acid consisting of 18 to 120 nucleotides". However, claims 1-3 as originally filed do not recite this size range, but rather recite that RNA encoded by the bioinformatically detectable novel gene is about 18 to about 24 nucleotides in length and originates from an RNA precursor which is about 50 to about 120 nucleotides in length; or RNA sections being about 50 to about 120 nucleotides in length and comprising an RNA segment that is about 18 to about 24 nucleotides in length. Originally filed claims 1-3 are consistent with the size ranges recited in the specification at paragraph 0015. Therefore, originally filed claims 1-3 and

paragraph 0015 of the specification do not teach a size limitation of a nucleic acid consisting of 18 to 120 nucleotides in length, as instantly recited.

The specification teaches that sequences designated SEQ ID NO: 1 through SEQ ID NO: 200 are nucleotide sequences of 200 gene precursors. As explained above, originally filed claims 1-3 and the specification at paragraph 0015 teach that precursors are about 50 to about 120 nculeotides in length.

Furthermore, applicant points to Table 2, lines 1116-1120 and paragraph 50905 for support for the newly added limitation that the sequence may comprise "at least 18 consecutive nucleotides of SEQ ID NO: 48" in claim 17. However, neither Table 2 nor paragraph 50905 of the instant specification disclose a limitation of "at least 18 consecutive nucleotides of SEQ ID NO: 48".

Applicant points to originally filed claim 1 and paragraph 50906 of the specification for support for the limitation "RNA equivalent" in claim 17. However, neither originally filed claim 1 nor paragraph 50906 of the specification teaches "RNA equivalent", as instantly recited.

Applicant points to Table 2, lines 1116-1120 and paragraph 26993 of the originally filed specification for support for the limitation "at least 64/84" in claim 17. However, neither Table 2 nor paragraph 26993 of the specification discloses this limitation.

Applicant points to originally filed claim 1 and paragraph 50906 of the specification for support for the limitation "the complement of any one of (a)-(c)" in claim

17. However, neither originally filed claim 1 nor paragraph 50906 of the specification teaches such a limitation.

Applicant points to Table 2, lines 1116-1120 and paragraph 50907 of the specification for support for the limitation "wherein the at least 18 nucleotides comprises the sequence of SEQ ID NO: 354" in claim 18. However, neither Table 2 nor paragraph 50907 of the specification teaches such a limitation. Applicant points to the same locations for support for claims 20-22 as 17-19, which is explained above.

Applicant points to Table 4, lines 110852-111681 for support for the limitation "the nucleic acid is at least 14/30 complementary", as recited in newly added claims 27 and 28. However, support is not evident for the limitation "at least 14/30 complementary".

Applicant points to paragraph 0024 of the specification for support for a vector comprising an insert, as recited in newly added claims 29 and 30. It is noted that paragraph 0024 of the specification does teach a limitation of a vector including the DNA, but does not teach vectors including RNA equivalents, as encompassed by claims 17 and 20 from which claims 29 and 30 depend, respectively. The gene expression inhibition system of claims 33 and 34 have this same problem because the claims depend from claims 29 and 30, respectively.

Similarly, applicant points to paragraph 0028 of the specification for support for a probe comprising an insert, as recited in newly added claims 31 and 32. It is noted that paragraph 0028 of the specification does teach a limitation of a probe including the DNA, but does not teach probes including RNA equivalents, as encompassed by claims

17 and 20 from which claims 31 and 32 depend, respectively. The gene expression detection system of claims 35 and 36 have this same problem because the claims depend from claims 31 and 32, respectively.

Furthermore, there is no support for each of the newly added claim limitations in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 11/24/03, which is the filing date of the instant application.

A review of the specification, and particularly at the pages pointed to by applicant, does not reveal support for where the various claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 11/6/06.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-22, 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Random Primer 24, sold by New England Biolabs (1998/99 New England Biolabs Catalog, see cover page, page 121 and page 284).

The instant claims are directed to an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence comprises (a) at least 18 consecutive nucleotides of SEQ ID NO: 48; (b) an RNA equivalent of (a); (c) a sequence at least 64/84 identical to (a) or (b); or (d) the complement of any one of (a)-(c). The at least 18 nucleotides comprises the sequence of SEQ ID NO: 354 and consists of 18 to 24 nucleotides. The claims are further directed to a probe comprising an insert consisting of the nucleic acid.

Random Primer 24 contains every possible 24-nucleotide sequence. The following calculations rely on facts provided on page 284 of the catalog, specifically the mass of 1.0 A_{260} unit of single-stranded DNA and the molecular weight of single-stranded DNA per nucleotide (i.e. half the weight of a double-stranded DNA per basepair):

Random 24-mer:

Molecular weight of 24-mer:
24×325 daltons/nucleotide = 7,800 daltons = 7,800 g/mol

Number of possible 24-mers:
$4^{24} = 2.8 \times 10^{14}$ molecules

How many molecules of 24-mer in a vial sold by NEB:
1 A_{260} unit = 33 μg = 3.3×10^{-5} g
3.3×10^{-5} g ÷ 7,800 g/mol = 4.2×10^{-9} mol
$(4.2 \times 10^{-9}$ mol) × $(6.02 \times 10^{23}$ molecules/mol) = 2.5×10^{15} molecules

How many vials needed to sum to 1 of each possible 24-mer:
2.8×10^{14} molecules ÷ 2.5×10^{15} molecules = 0.11 vial

Put another way, every vial of Random Primer 24 sold by New England Biolabs would be expected to contain 9 copies of every possible 24-nucleotide sequence. Therefore, Random Primer 24 would contain every possible gene fragment imaginable

that is 24 nucleotides in length, thus meeting the structural limitations of claims 17-22, 31 and 32.

The examiner notes the claims are drawn to an "isolated nucleic acid." However, no clear or limiting definition of the term "isolated" is readily found in the specification that would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Given the voluminous nature of the instant application, if applicant is aware of a definition of the term which would preclude compositions of the type referred to in the instant rejection, applicant is invited to point to such disclosure in replying to the instant rejection.

Accordingly, the Random Primer 24 sold by New England Biolabs anticipates the instant claims.

Claims 17, 20, 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Fussenegger et al. (US 6,287,813 B1).

The instant claims are directed to an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence comprises (a) at least 18 consecutive nucleotides of SEQ ID NO: 48; (b) an RNA equivalent of (a); (c) a sequence at least 64/84 identical to (a) or (b); or (d) the complement of any one of (a)-(c). The claims are further directed to a probe comprising an insert consisting of the nucleic acid.

Fussenegger et al. teach an isolated nucleic acid, more specifically a primer, wherein the nucleic acid is 101 nucleotides in length and comprises a sequence at nucleotides 49-77 that is 79.3% complementary to nucleotides 23-51 of instant SEQ ID

NO: 48, meeting the instant limitation of the complement of "a sequence at least 64/84" (or 76%) identical to at least 18 consecutive nucleotides of SEQ ID NO: 48. The nucleic acid sequence of Fussenegger et al. therefore meets the structural limitations of the instant claims.

Therefore, the instant invention is anticipated by Fussenegger et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-26, 31 and 32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 13 of copending Application No. 11/130,645. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of application '645 are directed to isolated nucleic acid sequences that overlap in

scope. The instantly recited sequences are anticipated by claim 1 of application '645. Specifically, SEQ ID NO: 13291 of application '645 is 100% identical to instant SEQ ID NO: 354 and SEQ ID NO: 3104 of application '645 is 84 nucleotides and length and comprises instant SEQ ID NO: 354. Furthermore, the instant claims and the claims of application '645 are directed to probes comprising the sequences. Instant claims 25 and 26 recite that the nucleic acid is capable of modulating expression of a target gene, whereas claim 13 of application '645 recites a method of inhibiting expression of a target gene with sequences within the scope of the instant invention. Therefore, the instant sequences and the sequences of application '645 are obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amy H. Bowman/
Patent Examiner
Art Unit 1635